REMARKS

Claims 1, 17-19, 23, 29, 34-38, 44, 47, and 54-63 are pending in this application. All of the claims are rejected under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. § 103(a) for obviousness. Claims 1, 17-19, 23, 29, 34-38, and 56-60 also stand rejected under the judicially created doctrine of obviousness-type double patenting. Each of the Office's rejections is addressed below. Applicants respectfully request reconsideration of the claims as amended.

Support for the amendments

Claims 1, 19, 37, 38, 44, 47, and 61 have been amended to recite that the antibodies include a variable region that consists of the recited SEQ ID NOs or mouse 13C4 or 11E10 antibody variable regions. Claims 19 and 61 have been amended to correct a typographical error in the ATCC number provided. The specification has also been amended to correct the error. Applicants provide herewith a copy of the ATCC catalog page (Exhibit A) demonstrating that the ATCC number for the mouse 11E10 hybridoma deposited by Dr. Alison O'Brien is ATCC CRL 1907. No new matter is added by these amendments.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 17-19, 23, 29, 34-38, 44, 47, and 54-63 are variously rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description and enablement rejections. Each of the rejections is addressed below.

Enablement

Claims 1, 17-19, 23, 29, 34-38, 44, 47, and 54-63 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In making the enablement rejection, the Examiner acknowledges that Applicants' specification enables humanized monoclonal antibodies that include variable regions consisting of the variable heavy and light chains of monoclonal antibodies 13C4 or 11E10, but maintains the rejection on the grounds that the specification does not enable humanized antibodies that specifically reacts with the Stx1 or Stx2 antigen wherein the heavy and light chains of the antibodies "comprise" the recited murine immunoglobulin variable regions. As applied to the current claims, this rejection may be withdrawn.

While not agreeing with the Examiner, in order to expedite prosecution, Applicants have amended the claims to recite the antibody species that the Examiner has indicated are enabled by the specification. Specifically, claims 1, 37, 38, and 44 have been amended to recite the limitation that the antibody includes a variable region that *consists of* the immunoglobulin heavy chain and light chain variable regions shown in

Figure 3 (SEQ ID NOs: 19 and 21) or the immunoglobulin heavy chain and light chain variable regions shown in Figure 6 (SEQ ID NOs: 42 and 44). Claims 19, 47, 56, and 61 recite the limitation that the antibody includes a variable region that *consists of* either the murine 11E10 (ATCC accession no. CRL 1907) or the murine 13C4 (ATCC CRL 1794) variable region. All remaining claims depend from one of these claims and, by definition, include the limitations to the defined variable regions.

As indicated by the Examiner at page 4 of the Office Action, the specification is enabling for "humanized monoclonal antibodies consisting of the variable heavy and light chains of monoclonal antibodies 13C4 or 11E10 (defined regions)." With regard to the asserted lack of enablement for the pharmaceutical compositions, the Examiner also states that the specification is enabling for "pharmaceutical compositions comprising humanized monoclonal antibodies with the variable light and heavy chains of monoclonal antibodies 13C4 or 11E10 (defined sequences)." (Office Action, page 7-8) In view of the amendments to the claims, Applicants submit that the enablement rejection can now be withdrawn.

Written Description

Claims 1, 17-19, 23, 29, 34-38, 44, 47, and 54-63, stand rejected under § 112, first paragraph, on the assertion that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art

that Applicants, at the time the application was filed, were in possession of the claimed invention.

While not agreeing with the Examiner, in order to expedite prosecution, Applicants have amended the claims to recite only the antibody species that the Examiner has indicated satisfy the written description requirement. The presently amended claims recite the limitation that the antibody includes immunoglobulin variable regions that consist of the 13C4 or 11E10 variable region as provided either by SEQ ID NOs: 19 and 21 or SEQ ID NOs: 42 and 44 or by the ATCC deposit number for the murine 13C4 and 11E10 antibodies.

As indicated by the Examiner at page 13-14 of the Office Action, "the specific antibodies that are produced from murine antibodies 13C4 and 11E10 (i.e., humanized antibodies whose variable light and heavy chains consist of the variable light and heavy chains of antibodies 13C4 and 11E10) meet the written description requirement." Accordingly, the rejection of claims 1, 17-19, 23, 29, 34-38, 44, 47, and 54-63 for failing to comply with the written description requirement can be withdrawn.

Rejections under 35 U.S.C. §103(a)

Claims 1, 17-19, 23, 29, 34-38, 44, 47, and 54-63 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Speirs et al. (*Canadian Journal of Microbiology*, 37:650-653, 1991; "Speirs") or O'Brien et al. (U.S. Patent No. 5,747,272; "O'Brien") in

view of Carter et al. (WO 94/04679; "Carter") or Shitara et al. (U.S. Patent No. 5,866,692; "Shitara") and further in view of Tzipori et al. (U.S. Patent Application Publication No. 2003/0082189; "Tzipori"). Speirs and O'Brien are cited for disclosing the mouse 13C4 and 11E10 antibodies. Carter and Shitara are relied upon for disclosing methods of producing humanized antibodies. Tzipori is cited for disclosing that monoclonal antibodies specific for Shiga toxins can be used to treat hemolytic uremic syndrome. Applicants respectfully traverse this rejection.

Applicants' invention features humanized monoclonal antibodies that specifically bind to Stx1 or Stx2 antigen. As presently amended, all of the claimed antibodies feature a human immunoglobulin constant region and a defined murine variable region. The defined murine variable regions consist of variable region sequences provided as either the SEQ ID NOs or by the ATCC deposit number of the anti-Stx1 or anti-Stx2 murine antibody. For example, claim 1, as amended, recites the limitation that the humanized monoclonal antibody includes a variable region that consists of the sequences provided in SEQ ID NOs: 19 and 21 (for binding to Stx1) or the sequences provided in SEQ ID NOs: 42 and 44 (for binding to Stx2). Claim 19, as amended, recites the limitation that the humanized monoclonal antibody that binds to Stx2 includes a variable region that consists of the murine 11E10 (ATCC Accession No. CRL 1907) variable region. Claim 47, as amended, recites the limitation that the humanized monoclonal antibody that binds to Stx1 includes a variable region that consists of the murine 13C4 (ATCC Accession No.

CRL 1794) variable region. Applicants submit that there is nothing in the references of record that provides a basis for selecting either 13C4 or 11E10 as a candidate antibody for humanization to arrive at the *defined antibodies as presently claimed.*

Speirs and O'Brien describe using the mouse 13C4 and 11E10 antibodies in a diagnostic kit for detecting Shiga-like toxins. There is nothing in Speirs or O'Brien that teaches, suggests, or motivates the skilled worker to use their antibodies in a therapeutic application to treat a Shiga toxin induced disease, much less a teaching to humanize these antibodies for that purpose. The ability of an antibody to detect a Shiga-like toxin in an *in vitro diagnostic assay* does not necessarily translate into an ability to effectively neutralize a Shiga-like toxin or protect an animal against a challenge with a Shiga toxin *in vivo* as shown for the claimed antibodies in Examples 7 and 8 of the present specification.

Carter and Shitara describe general methods for humanizing an antibody, and each fails to describe or mention either the 13C4 or 11E10 antibody.

The Examiner states that Tzipori provided the necessary motivation to humanize the antibodies "in order to use them in the treatment methodologies disclosed." Tzipori, however, fails to provide motivation to produce the claimed humanized 13C4 and 11E10 antibodies because Tzipori describes completely different antibodies and fails to even mention 13C4 or 11E10. Tzipori's teachings include methods for the treatment of hemolytic uremic syndrome using antibodies to Shiga like toxins (SLT-I and SLT-II) that are completely unrelated to the presently claimed antibodies. Tzipori describes the

generation of mouse monoclonal antibodies against Shiga-like toxins and provides one *in vivo* assay that includes the treatment of piglets with immune serum from piglets previously immunized with a Shiga like toxin. This therapeutic regimen did not include the use of mouse antibodies to Shiga like toxins, let alone the 13C4 or 11E10 antibodies, humanized or otherwise.

Moreover, Applicants point out that at the time Tzipori's priority application was filed, the 13C4 and 11E10 mouse monoclonal antibodies had been known in the art as diagnostic reagents for *over five years* (Speirs was published in August of 1991 and Tzipori's priority application was filed on November 15, 1996). Tzipori, however, chose to use completely different antibodies for the treatment of hemolytic uremic syndrome. The fact that Tzipori chose not to use the 13C4 and 11E10 antibodies or to humanize the 13C4 and 11E10 antibodies, although they were known in the art, underscores the nonobviousness of the humanized 13C4 and 11E10 antibodies as presently claimed. Applicants submit that a skilled artisan, upon reading Tzipori, would not be motivated to choose an antibody that Tzipori himself chose not to use, and to humanize that antibody in order to arrive at the presently claimed humanized antibodies or combination of antibodies.

Absent a motivation to choose the specific 13C4 and 11E10 antibodies for humanization, the Examiner has not shown a proper *prima facie* case of obviousness, and the rejection of the claims under § 103 for obviousness over Speirs or O'Brien in view of

Carter or Shitara and further in view of Tzipori should therefore be withdrawn.

Objective Indicia of Nonobviousness

Further, even if the combination of Speirs or O'Brien with Carter or Shitara and with Tzipori did establish a *prima facie* case of obviousness, which it does not, objective indicia can be used to overcome the rejection of claims 1, 17-19, 23, 29, 34-38, 44, 47, and 54-63 under 35 U.S.C. § 103(a) for obviousness. The M.P.E.P. § 716.01(a) states:

> Affidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103. The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983) that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." Such evidence might give light to circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or unobviousness, such evidence may have relevancy. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966); *In re Palmer*, 451 F.2d 1100, 172 USPQ 126 (CCPA 1971); *In re Fielder,* 471 F.2d 640, 176 USPQ 300 (CCPA 1973).

M.P.E.P. § 716.04 sets forth the three criteria for establishing a long felt need as follows:

> 1: The need must have been a persistent one that was recognized by those of ordinary skill in the art.
>
> 2: The long-felt need must not have been satisfied by another before the invention by applicant.

3: Third, the invention must in fact satisfy the long-felt need.

Applicants' specification teaches that there is a need for an agent that treats or prevents Shiga-toxin associated diseases including hemolytic uremic syndrome (HUS). HUS is characterized by acute renal failure, hemolytic anemia, fever, and thrombocytopenia, and is one of the most common causes of acute renal failure in children. Applicants also state that "currently there is no known cure or vaccine for ... HUS" and point out that "there is a need in the art to provide monoclonal antibodies that can bind to Shiga toxins which could prevent or lessen the devastating effects of these toxins." These facts, outlined in the specification, demonstrate that the need for an agent that treats or prevents Shiga-toxin associated diseases was a persistent one recognized by those in the art (criteria 1, above) and that this need has not been met by others (criteria 2, above).

Applicants' have designed antibodies that solve a problem scientists have been tackling for years. Indeed practitioners in the field immediately recognized that Applicants' antibodies represented a remarkable potential advance in treating HUS. As evidence of this assertion, Applicants direct the Examiner's attention to a letter (previously submitted as Exhibit B with the Reply filed on May 30, 2007) from the U.S. Food and Drug Administration (FDA) to Caprion Pharmaceuticals[1], the exclusive licensee

[1] Applicants note that Caprion Pharmaceuticals changed its name to Thallion Pharmaceuticals Inc. after acquiring Ecopia Biosciences Inc. on March 13, 2007.

of the present application. The FDA states that a clinical development program designed to utilize Applicants' claimed monoclonal antibodies to Shiga toxin has been granted "fast-track designation" for the treatment of Shiga toxin-producing bacterial infections. In granting fast-track designation, the FDA stated:

> [HUS] is a serious condition that may result from infection with Shiga toxin-producing bacteria. There are currently no therapies available for the prevention of this condition in infected patients. Chimeric monoclonal antibodies to Shiga toxins 1 and 2 have the theoretical potential to address this unmet medical need.

Clearly the FDA notes that there is an "unmet medical need" for treating infections resulting from Shiga toxin producing bacteria (criteria 1 and 2, above.) Moreover, the FDA makes clear that Applicants' antibodies address this unmet need (criteria 3, above.) The FDA's recognition that Applicants' antibodies deal with an unmet medical need, and that these antibodies represent a remarkable advance in the field, is indicative of invention. Applicants have satisfied all three of the criteria set forth in MPEP § 716.04 for establishing a long felt need and submit that these objective indicia should be considered by the Examiner as a further basis for overcoming the obviousness rejection.

Applicants note that in the present Office Action, the Examiner states that, "while the instant invention may "address" an unmet medical need, they have not been demonstrated to "satisfy" it as required by MPEP § 716.04." In response, Applicants note that clinical trials are underway and Applicants intend to provide these results to the

Office when available.

Another objective indicium of non-obviousness that must be considered in determining the patentability of an invention is recognition for the invention by those in the field. In the present case, this invention has been the subject of professional recognition. As is noted above, the FDA has recognized the discovery of Applicants' claimed humanized antibodies as having a significant impact on the treatment of HUS, granting "fast track designation" to the clinical development program designed to utilize the claimed monoclonal antibodies to Shiga toxin. Such an acknowledgment demonstrates professional recognition of Applicants' claimed invention, and is strong support for nonobviousness.

For these reasons as well, Applicants respectfully request that the rejection of claims 1, 17-19, 23, 29, 34-38, 44, 47, and 54-63 under § 103 for obviousness be withdrawn.

Rejections under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 1, 17-19, 23, 29, 34-38, and 56-60 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272 ("the '272 patent") in view of Carter et al. (WO 94/04679; "Carter"). Applicants traverse this rejection.

In the present case, the Examiner rejects claims 1, 17-19, 23, 29, 34-38, and 56-60 for obviousness-type double patenting over claim 9 of the '272 patent in view of Carter. Claim 9 of the '272 patent depends from claim 1 and both are reproduced below.

> 1. A diagnostic kit for the detection of Shiga-like toxins comprising
>
> an SLT antibody reagent comprising an antibody specific to Shiga-like toxin, type I, and an antibody specific to Shiga-like toxin, type II, in aqueous solution; and
>
> a detection reagent comprising a chemiluminescent 2,3-dihydro-1,4-phthalizinedione and a sensitivity enhancer capable of enhancing the sensitivity of the chemiluminescent 2,3-dihydro-1,4-phthalizinedione reaction.
>
> 9. The diagnostic kit of claim 1 wherein the antibody specific to Shiga-like toxin, type I, is 13C4, produced by ATCC CRL 1794 and the antibody specific to Shiga-like toxin, Type II is 11E10 produced by ATCC CRL 1907.

Claims 1, 17-19, 23, 29, 34-38, and 56-60 feature humanized monoclonal antibodies that specifically bind to a Shiga toxin protein and pharmaceutical compositions that include the humanized monoclonal antibodies. The Examiner states that, "it would have been obvious for the skilled artisan to humanize the antibodies of patent 5,747,272 to minimize the side effects of murine antibodies." (Office Action, page 3) Applicants fail to understand how minimization of the side effects relates to the diagnostic kits as claimed in claim 9 of the '272 patent. Applicants submit that the Examiner has not provided a clear basis for the rejection of claims 1, 17-19, 23, 29, 34-38, and 56-60 under

the judicially created doctrine of obviousness-type double patenting over claim 9 of the '272 patent and request clarification on this point.

In response to the Examiner's assertion that it would have been obvious for the skilled artisan to humanize the antibodies of the '272 patent to minimize the side effects of murine antibodies, Applicants submit that Carter fails to establish that one skilled in the art, in view of the '272 patent, would be motivated to modify the teachings of claim 9 of the '272 patent to arrive at the presently claimed invention. Neither claim 9 nor Carter provides motivation for humanization of the mouse 13C4 or 11E10 antibodies. Claim 9 is directed to a diagnostic kit that includes the mouse 13C4 and 11E10 antibodies and Carter simply discloses methods of producing humanized antibodies. In addition, Applicants present strong evidence of the nonobviousness of the presently claimed invention. The nonstatutory obviousness-type double patenting rejection over claim 9 of the '272 patent in view of Carter should be withdrawn.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance and such action is respectfully requested.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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